JACC: ADVANCES VOL. 3, NO. 2, 2024

EDITORIAL COMMENT

Vitamin D and Cardiovascular Risk

Stemming the Tide of Poor Outcomes in Coronary Heart Disease*

Gian Paolo Fadini, MD, PhD,[a,b] Marella Marassi, MD[a]

Vitamin D deficiency (VDD) is highly prevalent in the general population, reaching up to 50% in areas with limited sunlight exposure. Being a vitamin D (VD) receptor widely expressed across human tissues, it is understandable that VDD is associated with a variety of disparate changes in multiple organs, not limited to the calcium-phosphate metabolism and bone health.

The epidemiological association between VDD and cardiometabolic diseases has fueled intense research in the quest to tackle the cardiovascular risk burden. Indeed, observational studies have consistently found a heightened incidence of various cardiometabolic conditions, including hypertension, stroke, diabetes, coronary heart disease, and cardiovascular mortality among individuals with VDD.[1] The activation of the renin-angiotensin-aldosterone system, secondary hyperparathyroidism, and atherogenesis exacerbation are some of the potential mechanisms for the increased cardiovascular risk in VDD.[1] However, causality linking VDD to cardiovascular diseases (CVDs) is not yet established; randomized trials testing VD supplementation have overall failed to ameliorate cardiometabolic outcomes. To date, VD supplement strategies have shown no benefits on blood pressure, incident diabetes, stroke, myocardial infarction, and cardiovascular mortality; hence, their use for cardiovascular protection remains questionable.[2]

Should we then discard VDD as an innocent bystander of cardiovascular risk or try to dissect its role further?

In this issue of *JACC: Advances*, Desai et al[3] provide new exciting evidence to help redefine who could benefit from targeted VD supplementation. By analyzing a large cohort of patients with coronary heart disease from the Emory Cardiovascular Biobank, the authors confirmed the association between VDD and an excess risk of major adverse cardiovascular events and cardiovascular and all-cause mortality, with a cut-point at the traditional VD level of <20 ng/dL. The association was independent from confounders and consistent across some strata of the population. Of note, participants with VDD exhibited significant elevations in high-sensitive C-reactive protein (hsCRP), the prototypical inflammatory cardiovascular risk biomarker and a predictor of adverse outcomes.

Although enhanced inflammation has been consistently associated with both VDD and CVD,[4] available data regarding the effects of VD supplementation on hsCRP levels are inconclusive, even in populations at high cardiovascular risk.[5-7] At present, whether VD supplementation diminishes hsCRP and whether this in turn mediates cardiovascular protection remains controversial.

Despite VDD and high hsCRP were correlated, each predicted incident adverse events independently from the other, and individuals with both VDD and high hsCRP displayed the worst outcome. This finding implies an interaction between VDD and inflammation in determining cardiovascular risk, but Desai et al went further and built on the recent understanding that chronic low-grade inflammation impinges upon the endogenous organism's self-repair

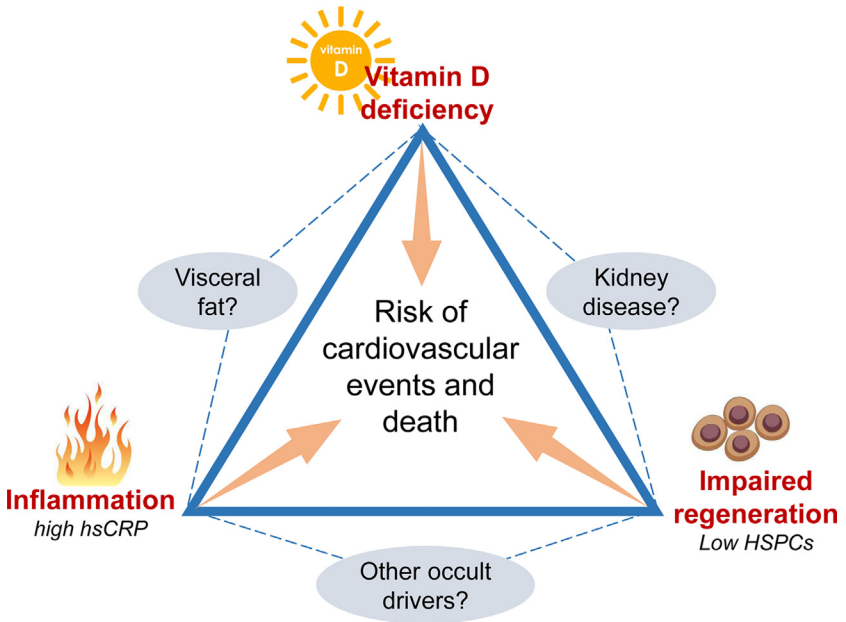
*Editorials published in *JACC: Advances* reflect the views of the authors and do not necessarily represent the views of *JACC: Advances* or the American College of Cardiology.

From the [a]Department of Medicine, University of Padova, Padua, Italy; and the [b]Veneto Institute of Molecular Medicine, Padua, Italy.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2023.100803

FIGURE 1 The Triangulation Between Vitamin D Deficiency, Chronic Inflammation, and Impaired Regenerative Capacity



The risk for cardiovascular disease lies in the middle of this triangle and is contributed by each of the triangle corners. The figure illustrates excess visceral fat and kidney disease as possible additional drivers and leaves space for occult drivers that have yet to be elucidated. hsCRP = high-sensitive C-reactive protein; HSPC = hematopoietic stem/progenitor cell.

capacity. The levels of circulating $CD34^+$ cells, mostly representing hematopoietic stem/progenitor cells (HSPCs), represent such regenerative capacity because human $CD34^+$ cells aid vascular repair.[8] In addition, several cohort studies show that individuals with cardiovascular, metabolic, or kidney disease exhibit poorer outcomes when they have low circulating $CD34^+$ cells, including excess all-cause mortality.[9] This was confirmed by the authors in their cohorts. However, contrary to a prior study showing a direct correlation between VD and $CD34^+$ cell subsets,[10-12] the authors here reported no association between VDD and HSPC levels. This seems to suggest that VDD and low HSPCs are totally independent drivers of cardiovascular risk.

Probably the paper's most outstanding finding is the exceptionally high cardiovascular risk conferred by the simultaneous presence of VDD, high hsCRP, and low HSPCs in the same individuals. Such a deadly triangulation (**Figure 1**) deserves special attention as the paper's most notable output.

While the authors provide no hint on the association between hsCRP and HSPCs, there is now considerable evidence that inflammation underlies the shortage of circulating HSPCs. Myelopoiesis in the bone marrow elicits autocrine/paracrine signals within the stem cell niche that impede HSPCs from reaching the bloodstream.[13] HSPC levels are susceptible to therapeutic manipulation[14] and cardiovascular even rates can be reduced with anti-inflammatory therapies,[15] but there is still no evidence that countering inflammation rescues HSPC levels and that this contributes to cardiovascular protection.

Along the other side of the triangle, a connection between VDD and circulating HSPC levels would be intriguing in view of the role of VD in bone homeostasis. As HSPCs are released into the circulation from their bone marrow niches, conditions affecting bone integrity, like VDD, could disrupt the HSPC niche and impair their mobilization. Also, circulating progenitor cells have been implicated in the so-called bone-vascular axis to explain the co-occurrence of osteoporosis and vascular calcification, driving cardiovascular events. Indeed, circulating progenitors can undergo a pro-calcific drift characterized by expression of typical bone-related markers.[16] Desai et al[3] did not examine $CD34^+$ cell phenotype in more detail to assess whether VDD was characterized by osteogenic differentiation, but this is an area of possible future investigation because VDD may change $CD34^+$ cell properties more than their levels.

Furthermore, this apparent triangle may hide occult drivers of CVD. First, while the authors controlled for the effect of body mass index, they did not consider visceral adiposity, which is a cause of VDD and a determinant of inflammation and HSPC traffic.[17] Second, chronic kidney disease seems to be an obvious common denominator of VDD, inflammation, and HSPC defects. Recently, we found that patients with diabetic kidney disease present with low HSPCs, and HSPC pauperization, in turn, predicted worsening of kidney function.[18] Whether VDD plays any role in this process is worth investigating.

In the end, we are still left with the possibility that each of the tree corners of the triangle are just epiphenomena of a hitherto unidentified factor and that we should target such core mechanism(s) instead of its visible manifestations.

Meanwhile, it is fascinating that, when combined with inflammation and hindered regenerative capacity, VDD projects its detrimental cardiovascular effect sky high. In line with the modern precision medicine paradigm, in place of a one-fits-all strategy of VDD correction, we have a new target population of patients for VD supplementation in future studies.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This study was supported by institutional grants from the University of Padova. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Professor Gian Paolo Fadini, Department of Medicine, University of Padova, Via Giustiniani 2, 35128 Padua, Italy. E-mail: gianpaolo.fadini@unipd.it.

REFERENCES

1. Lee JH, O'Keefe JH, Bell D, Hensrud DD, Holick MF. Vitamin D deficiency an important, common, and easily treatable cardiovascular risk factor? *J Am Coll Cardiol*. 2008;52(24):1949–1956.

2. Michos ED, Cainzos-Achirica M, Heravi AS, Appel LJ, Vitamin D. Calcium supplements, and implications for cardiovascular health: JACC focus seminar. *J Am Coll Cardiol*. 2021;77(4):437–449.

3. Desai SR, Ko Y, Liu C, et al. Vitamin D deficiency, inflammation, and diminished endogenous regenerative capacity in coronary heart disease. *JACC: Adv*. 2024;3:100804.

4. Yin K, Agrawal DK. Vitamin D and inflammatory diseases. *J Inflamm Res*. 2014;7:69–87.

5. Shab-Bidar S, Neyestani TR, Djazayery A, et al. Improvement of vitamin D status resulted in amelioration of biomarkers of systemic inflammation in the subjects with type 2 diabetes. *Diabetes Metab Res Rev*. 2012;28(5):424–430.

6. Jamka M, Woźniewicz M, Walkowiak J, Bogdański P, Jeszka J, Stelmach-Mardas M. The effect of vitamin D supplementation on selected inflammatory biomarkers in obese and overweight subjects: a systematic review with meta-analysis. *Eur J Nutr*. 2016;55(6):2163–2176.

7. Rodriguez AJ, Mousa A, Ebeling PR, Scott D, de Courten B. Effects of vitamin D supplementation on inflammatory markers in heart failure: a systematic review and meta-analysis of randomized controlled trials. *Sci Rep*. 2018;8(1):1169.

8. Fadini GP, Mehta A, Dhindsa DS, et al. Circulating stem cells and cardiovascular outcomes: from basic science to the clinic. *Eur Heart J*. 2020;41(44):4271–4282.

9. Rigato M, Avogaro A, Fadini GP. Levels of circulating progenitor cells, cardiovascular outcomes and death: a meta-analysis of prospective observational studies. *Circ Res*. 2016;118(12):1930–1939.

10. Yiu YF, Chan YH, Yiu KH, et al. Vitamin D deficiency is associated with depletion of circulating endothelial progenitor cells and endothelial dysfunction in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2011;96(5):E830–E835.

11. Pouresmaeil V, Ebre S, Yazdi MS. Assessment of the relationship between CD34 antigen and vitamin D level and insulin resistance in patients with type 2 diabetes. *Clin Diabetes*. 2022;40(4):425–433.

12. Lo Gullo A, Mandraffino G, Bagnato G, et al. Vitamin D status in rheumatoid arthritis: inflammation, arterial stiffness and circulating progenitor cell number. *PLoS One*. 2015;10(8):e0134602.

13. Fadini GP, Albiero M. Impaired hematopoietic stem/progenitor cell traffic and multi-organ damage in diabetes. *Stem Cells*. 2022;40(8):716–723.

14. Fadini GP, Avogaro A. Potential manipulation of endothelial progenitor cells in diabetes and its complications. *Diabetes Obes Metab*. 2010;12(7):570–583.

15. Ridker PM, Everett BM, Thuren T, et al. Anti-inflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med*. 2017;377(12):1119–1131.

16. Fadini GP, Rattazzi M, Matsumoto T, Asahara T, Khosla S. Emerging role of circulating calcifying cells in the bone-vascular axis. *Circulation*. 2012;125(22):2772–2781.

17. Fadini GP, Bonora BM, Marcuzzo G, et al. Circulating stem cells associate with adiposity and future metabolic deterioration in healthy subjects. *J Clin Endocrinol Metab*. 2015;100(12):4570–4578.

18. Bonora BM, Morieri ML, Marassi M, Cappellari R, Avogaro A, Fadini GP. Improved prediction of long-term kidney outcomes in people with type 2 diabetes by levels of circulating haematopoietic stem/progenitor cells. *Diabetologia*. 2023;66(12):2346–2355.

KEY WORDS bone, regeneration, stem cells, vascular disease